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Emergency Neurological Life Support: Airway, Ventilation, and Sedation

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Abstract Airway management and ventilation are central to the resuscitation of the neurologically ill. These patients often have evolving processes that threaten the airway and adequate ventilation. Furthermore, intubation, ventilation, and sedative choices directly affect brain perfusion. Therefore, Airway, Ventilation, and Sedation was chosen as an Emergency Neurological Life Support protocol. Topics include airway management, when and how to intubate with special attention to hemodynamics and preservation of cerebral blood flow, mechanical ventilation settings and the use of sedative agents based on the patient's neurological status.

Keywords Airway · Ventilation · Sedation · Neurocritical care · Emergency

Introduction

Intubation of the acutely brain injured patient can be a matter of life or death. Failure to intubate a patient with rapidly progressive neurological decline may result in respiratory arrest, secondary brain injury from hypoxia, acidosis, elevated intracranial pressure, or severe aspiration pneumonitis and acute respiratory distress syndrome. Conversely, the process of induction and intubation can elevate intracranial hypertension when a mass lesion is present, complete a massive infarction when brain tissue is marginally perfused, and result in temporary loss of the neurological examination at a time when neurological and neurosurgical decision-making is required.

The goals of airway management in neurological patients are to maintain adequate (but not excessive) oxygenation and ventilation, preserve cerebral perfusion, and prevent aspiration. A neurological assessment prior to the administration of sedating and paralyzing medications should be performed to provide a functional baseline, whereby neurological and neurosurgical decision making may ensue.

The ENLS suggested algorithm for the initial management of airway, ventilation, and sedation is shown in Fig. 1. Suggested items to complete within the first hour of evaluating a patient are shown in Table 1.

Assessing the Need for Intubation

Patients in severe respiratory distress or impending arrest should be intubated without delay. Additionally, a patient who cannot "protect his airway" because of depressed mental status or vomiting with aspiration may need tracheal intubation. Intubation has the potential for complications, creates significant hemodynamic disturbances, and should not be undertaken without a risk benefit assessment. However, it should not be delayed when necessary. The decision to intubate is influenced by factors specific to patient physiology, clinical environment, and the anticipated course of care.

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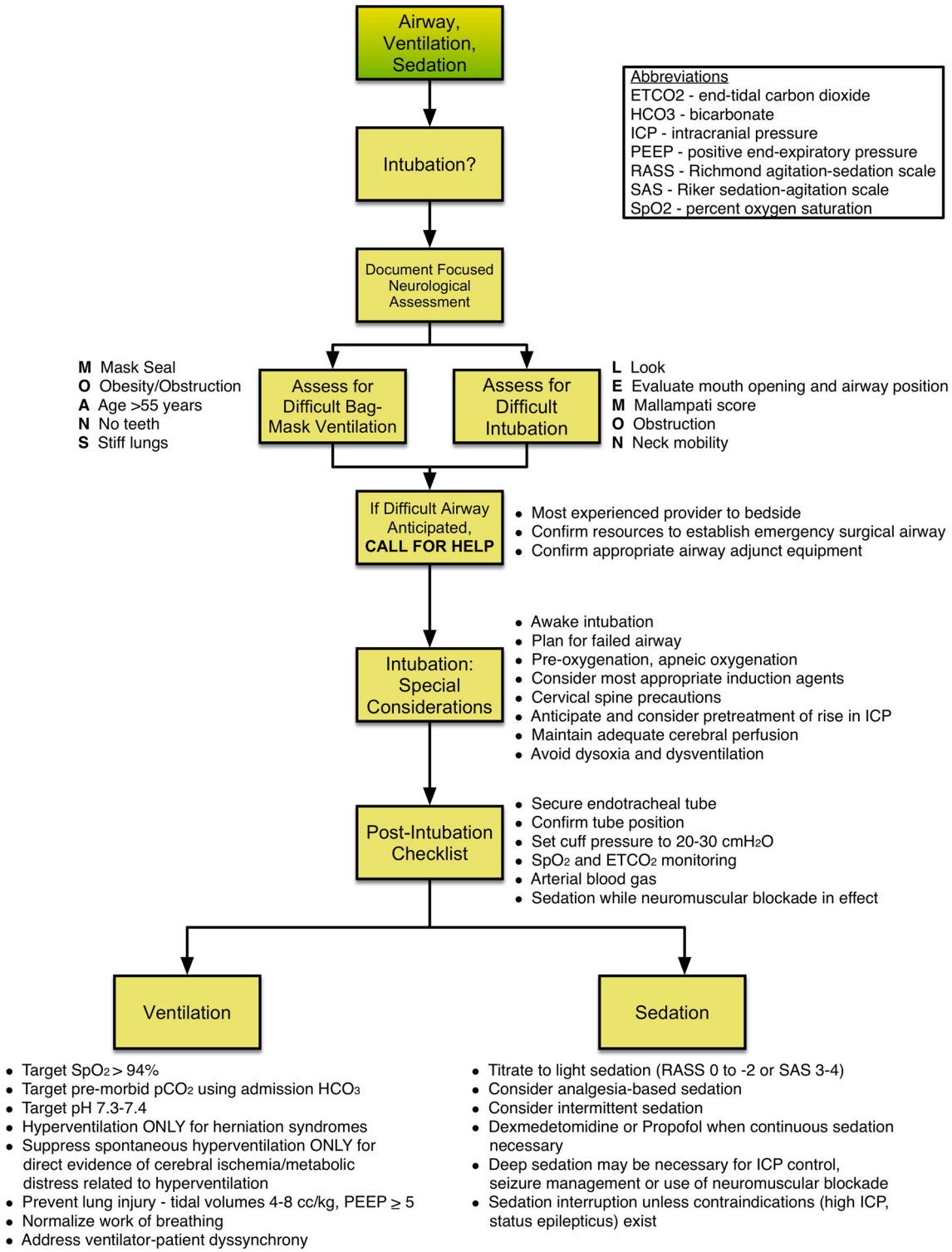
Airway, Ventilation, Sedation
Intubation?
Document Focused Neurological Assessment
Abbreviations
ETCO2 - end-tidal carbon dioxide
HCO3 - bicarbonate
ICP - intracranial pressure
PEEP - positive end-expiratory pressure
RASS - Richmond agitation-sedation scale
SAS - Riker sedation-agitation scale
SpO2 - percent oxygen saturation
M Mask Seal
O Obesity/Obstruction
A Age >55 years
N No teeth
S Stiff lungs
Assess for Difficult Bag-Mask Ventilation
Assess for Difficult Intubation
L Look
E Evaluate mouth opening and airway position
M Mallampati score
O Obstruction
N Neck mobility
If Difficult Airway Anticipated, CALL FOR HELP
Most experienced provider to bedside
Confirm resources to establish emergency surgical airway
Confirm appropriate airway adjunct equipment
Intubation: Special Considerations
Awake intubation
Plan for failed airway
Pre-oxygenation, apneic oxygenation
Consider most appropriate induction agents
Cervical spine precautions
Anticipate and consider pretreatment of rise in ICP
Maintain adequate cerebral perfusion
Avoid dysoxia and dysventilation
Post-Intubation Checklist
Secure endotracheal tube
Confirm tube position
Set cuff pressure to 20-30 cmH2O
SpO2 and ETCO2 monitoring
Arterial blood gas
Sedation while neuromuscular blockade in effect
Ventilation
Target SpO2 > 94%
Target pre-morbid pCO2 using admission HCO3
Target pH 7.3-7.4
Hyperventilation ONLY for herniation syndromes
Suppress spontaneous hyperventilation ONLY for direct evidence of cerebral ischemia/metabolic distress related to hyperventilation
Prevent lung injury - tidal volumes 4-8 cc/kg, PEEP ≥ 5
Normalize work of breathing
Address ventilator-patient dyssynchrony
Sedation
Titrate to light sedation (RASS 0 to -2 or SAS 3-4)
Consider analgesia-based sedation
Consider intermittent sedation
Dexmedetomidine or Propofol when continuous sedation necessary
Deep sedation may be necessary for ICP control, seizure management or use of neuromuscular blockade
Sedation interruption unless contraindications (high ICP, status epilepticus) exist

Fig. 1 ENLS airway, ventilation, and sedation protocol

In the emergency department (ED) or prehospital environment, a stuporous or comatose patient with an unknown diagnosis requiring extended transport, transfer, imaging, or invasive procedures may be most appropriately managed with a secure endotracheal airway. The same patient with a known condition, an anticipated stable or improving course, and no planned transportation may not require intubation and might be managed by a more conservative approach.

Table 1 Airway, ventilation, and sedation checklist within the first hour

Checklist
☐ Assess the need for intubation or non-invasive positive pressure ventilation
☐ Perform and document a focused neurological assessment prior to intubation
☐ Verify the endotracheal tube position
☐ Determine ventilation and oxygenation targets, and verify with ABG/SpO_2/$ETCO_2$
☐ Assess the need for analgesia and/or sedation in mechanically ventilated patients

With these considerations in mind, there are four commonly accepted indications to intubate:

Failure to Oxygenate

This finding may be determined by pulse oximetry (limitations include regional or systemic hypoperfusion, severe anemia, and opaque nail polish), arterial blood gas analysis, or the patient's visual appearance (cyanosis).

Failure to Ventilate

Ventilation is assessed by capnometry through nasal cannula or transcutaneous monitoring [1], arterial blood gas analysis, or gross visual appearance (excessive or inadequate work of breathing).

Failure to Protect the Airway

Airway protection is the result of numerous variables including bulbar function, airway anatomy, quantity and quality of secretions, strength of cough reflex, and ability to swallow after suctioning [2]. The presence of a gag reflex is an inadequate method of assessing airway protection [3].

Anticipated Neurological or Cardiopulmonary Decline Requiring Transport or Immediate Treatment

Anticipation of the trajectory of the patient's condition can avoid rushed or emergent intubations and allow for appropriate preparation for the procedure.

Decision Made to Intubate: Perform Neurological Assessment

Whenever possible, urgent management of the airway should coincide with a focused neurological assessment. The examination can typically be conducted in 2 min or less. The pre-sedation/pre-intubation neurologic exam establishes a baseline that is used to assess therapeutic interventions (e.g., patients with stroke, seizures, hydrocephalus or other disorders) or may identify injuries that are at risk of progressing (e.g., unstable cervical spine fractures). The assessment identifies the type of testing required and may help to limit unnecessary interventions, such as radiological cervical spine clearance. In general, the pre-intubation neurological assessment is the responsibility of the team leader who is coordinating the resuscitation. Findings should be documented and communicated directly to the team that assumes care of the patient. The pre-intubation neurological examination includes an assessment of:

- Level of arousal, interaction, and orientation, as well as an assessment of simple cortical functions such as vision, attention, and speech comprehension and fluency.
- Cranial nerve function.
- Motor function of each individual extremity.
- Tone and reflexes.
- Recognition of involuntary movement consistent with tremor or epileptic activity.
- Cervical tenderness or gross spinal abnormality.
- Sensory level in patients with suspected spinal cord injury.

Airway Assessment

A difficult airway may be broadly defined as an endotracheal intubation attempt in which a provider who is appropriately trained in airway management experiences difficulty with bag-mask ventilation, tracheal intubation or both [4]. Using this broad definition, up to 30% of ED intubations may involve "difficult airways" [5]. Patients with acute neurological injury may be particularly likely to have a difficult airway, because of the need to immobilize the cervical spine in patients who suffer trauma or are "found down" following neurological emergencies such as strokes and seizures. It is essential that all healthcare providers who manage critically ill neurological patients be able to identify common factors that may increase the complexity of airway management. Identification of the difficult airway is essential for selection of the appropriate technique (awake fiberoptic vs rapid sequence induction), tools (video vs direct laryngoscopy) and operator (anesthesiologist vs other provider, attending vs trainee). Failure

to identify a difficult airway prior to induction is one of the most important factors predicting a subsequent failed airway during the intubation attempt [6, 7].

The "LEMON" pneumonic has been shown to successfully predict difficult tracheal intubation in the emergency department [3, 8]:

L = Look externally, for features such as abnormal facies, oro-maxillo-facial trauma and abnormal body habitus.
E = Evaluate with the **3-2-2 rule**.

- Will **3** of the patient's fingers fit between the incisors of the open mouth? If not, mouth opening may be too limited to permit adequate laryngoscopic visualization or manipulation of the endotracheal tube.
- Will **3** of the patient's fingers fit between the chin (mentum) and the hyoid bone? If not, the airway may be too anterior for easy visualization with direct laryngoscopy (DL).
- Will **2** of the patient's fingers fit between the hyoid bone and the superior thyroid notch? If not, the airway may be too high in the neck to permit easy visualization.

M = Mallampati score assesses the extent of mouth opening in relation to tongue size [9, 10].

Grade I: Soft palate, entire uvula, faucial pillars visible.
Grade II: Soft palate, entire uvula visible.
Grade III: Soft palate, base of uvula visible.
Grade IV: Only hard palate visible.

Grades 1 and 2 predict easy visualization, 3 predicts difficulty and 4 extreme difficulty. Mallampati grading ideally requires some patient co-operation and may be difficult to assess in patients with acute brain injury.

O = Obstruction/obesity. The presence of redundant soft tissue (obesity), a supraglottic mass or trauma/hematoma within the oropharynx may obscure the view of the glottis.
N = Neck mobility. Inability to attain the sniffing position because of immobilization of the cervical spine in the trauma patient, ankylosing spondylitis, rheumatoid arthritis or age related degenerative disease.

The "MOANS" pneumonic predicts difficulty of bag mask ventilation [3]:

M = Mask seal, may be compromised by abnormal facies, facial hair and body fluids.
O = Obesity/obstruction.
A = Age >55.
N = No teeth.
S = Stiff lungs.

When a difficult airway is identified, the most important next step is to call for help, as appropriate. The provider with the most experience in airway management should be present at the bedside, as well as a provider capable of rapidly establishing a surgical (or percutaneous) airway in the event of a failed intubation. Availability of all necessary tools at the bedside, such as a supraglottic airway, endotracheal tube introducer (bougie), cricothyroidotomy tray, and a video laryngoscope should be confirmed. Finally, it is important to remember that prediction of a difficult airway is imperfect and that an *unanticipated* difficult airway may be encountered [11]. Ready availability of the necessary expertise and equipment in the form of an institutional airway team may increase survival to hospital discharge and decrease the need for a surgical airway [12, 13].

Endotracheal Intubation in the Critically Ill Neurological Patient

Several societies have published guidelines for the management of the difficult airway, particularly in the setting of anesthesia for elective procedures [4, 14–16]. Intubation of the critically ill patient is a fundamentally different clinical situation than intubation in the relatively stable environment of the operating room [16]. While over 90% will be technically successful, about 20–25% of critically ill patients will develop severe hypoxemia during intubation, 10–25% will develop severe hypotension and about 2% will suffer cardiac arrest [7, 17–19]. More so than other critically ill patients, the patient with acute brain injury is unlikely to tolerate significant periods of hypoxia or hypotension, which may result in secondary injury to the vulnerable brain [20–26]. The ENLS intubation algorithm, therefore, emphasizes evidence-based best practice for maintenance of adequate oxygenation and perfusion during intubation, as well as the most direct and dependable pathway to a definitive airway for providers with varied experience and backgrounds.

As a first step, at least 2 providers, including at least one provider experienced in airway management, should be present at the bedside. Two-provider presence may decrease complications associated with intubation of the critically ill [17, 27] (Fig. 2).

Awake Intubation

The provider may be "forced to act" in the patient with acute neurological illness who has a compromised airway and rapid progression to cardiovascular or respiratory collapse, necessitating an urgent attempt at laryngoscopy

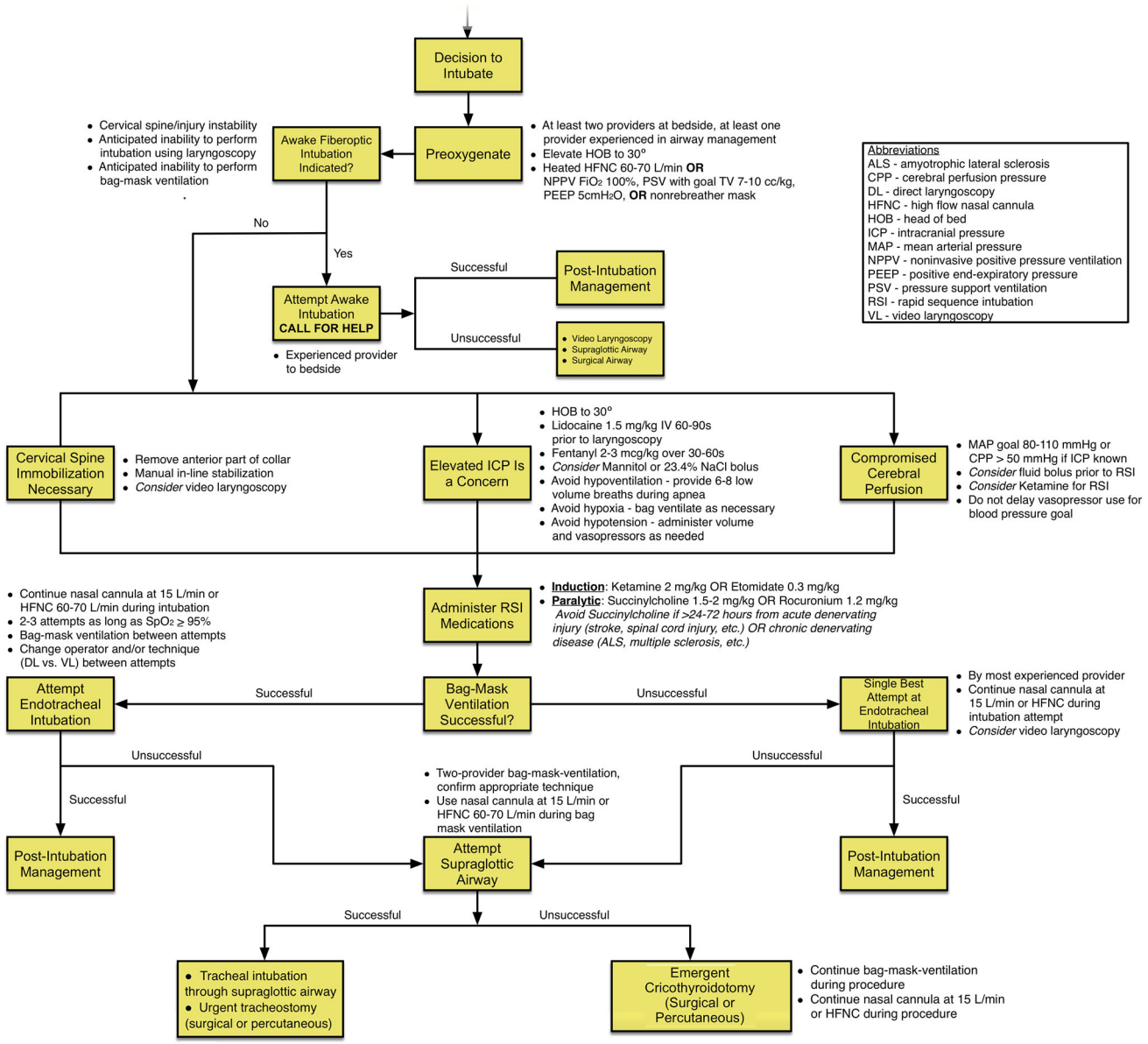
Decision to Intubate
Preoxygenate
At least two providers at bedside, at least one provider experienced in airway management
Elevate HOB to 30°
Heated HFNC 60-70 L/min OR NPPV FiO2 100%, PSV with goal TV 7-10 cc/kg, PEEP 5cmH2O, OR nonrebreather mask
Awake Fiberoptic Intubation Indicated?
Cervical spine/injury instability
Anticipated inability to perform intubation using laryngoscopy
Anticipated inability to perform bag-mask ventilation
No
Yes
Attempt Awake Intubation CALL FOR HELP
Experienced provider to bedside
Successful
Post-Intubation Management
Unsuccessful
Video Laryngoscopy
Supraglottic Airway
Surgical Airway
Abbreviations
ALS - amyotrophic lateral sclerosis
CPP - cerebral perfusion pressure
DL - direct laryngoscopy
HFNC - high flow nasal cannula
HOB - head of bed
ICP - intracranial pressure
MAP - mean arterial pressure
NPPV - noninvasive positive pressure ventilation
PEEP - positive end-expiratory pressure
PSV - pressure support ventilation
RSI - rapid sequence intubation
VL - video laryngoscopy
Cervical Spine Immobilization Necessary
Remove anterior part of collar
Manual in-line stabilization
Consider video laryngoscopy
Elevated ICP Is a Concern
HOB to 30°
Lidocaine 1.5 mg/kg IV 60-90s prior to laryngoscopy
Fentanyl 2-3 mcg/kg over 30-60s
Consider Mannitol or 23.4% NaCl bolus
Avoid hypoventilation - provide 6-8 low volume breaths during apnea
Avoid hypoxia - bag ventilate as necessary
Avoid hypotension - administer volume and vasopressors as needed
Compromised Cerebral Perfusion
MAP goal 80-110 mmHg or CPP > 50 mmHg if ICP known
Consider fluid bolus prior to RSI
Consider Ketamine for RSI
Do not delay vasopressor use for blood pressure goal
Continue nasal cannula at 15 L/min or HFNC 60-70 L/min during intubation
2-3 attempts as long as SpO2 ≥ 95%
Bag-mask ventilation between attempts
Change operator and/or technique (DL vs. VL) between attempts
Administer RSI Medications
Induction: Ketamine 2 mg/kg OR Etomidate 0.3 mg/kg
Paralytic: Succinylcholine 1.5-2 mg/kg OR Rocuronium 1.2 mg/kg
Avoid Succinylcholine if >24-72 hours from acute denervating injury (stroke, spinal cord injury, etc.) OR chronic denervating disease (ALS, multiple sclerosis, etc.)
Attempt Endotracheal Intubation
Successful
Bag-Mask Ventilation Successful?
Unsuccessful
Single Best Attempt at Endotracheal Intubation
By most experienced provider
Continue nasal cannula at 15 L/min or HFNC during intubation attempt
Consider video laryngoscopy
Unsuccessful
Successful
Two-provider bag-mask-ventilation, confirm appropriate technique
Use nasal cannula at 15 L/min or HFNC 60-70 L/min during bag mask ventilation
Unsuccessful
Successful
Post-Intubation Management
Attempt Supraglottic Airway
Post-Intubation Management
Successful
Unsuccessful
Tracheal intubation through supraglottic airway
Urgent tracheostomy (surgical or percutaneous)
Emergent Cricothyroidotomy (Surgical or Percutaneous)
Continue bag-mask-ventilation during procedure
Continue nasal cannula at 15 L/min or HFNC during procedure

Fig. 2 Algorithm for tracheal intubation of the critically ill neurological patient

and intubation. When the provider is not "forced to act", however, and the patient is spontaneously breathing and oxygenating adequately on supplemental oxygen, consideration should be given first to an awake intubation. An awake fiberoptic intubation will avoid the displacement of the cervical spine that is inevitable with the use of any laryngoscope, [28] and may be the intubation technique of choice in the presence of significant cervical spine injury. An awake intubation may also be the procedure of choice when an anticipated difficult airway or bag-mask ventilation makes cessation of spontaneous respiratory effort with rapid sequence intubation (RSI) hazardous. Awake intubation is typically performed using moderate sedation in conjunction with topical anesthesia, most commonly with a flexible endoscope that is navigated into the trachea via an oral or nasal route [29]. An endotracheal tube fitted onto the flexible endoscope is then advanced over the endoscope into the trachea. An awake intubation is not appropriate in patients with elevated intracranial pressure. A fiberoptic intubation requires considerable expertise, and should be performed only with a highly experienced provider at the bedside. Should awake intubation be unsuccessful, the experienced provider must decide on an alternative technique with the greatest likelihood of success, and may consider video laryngoscopy, a supraglottic airway, or a surgical airway.

Pre-oxygenation and Apneic Oxygenation

Maintaining an adequate oxygen saturation during intubation is critical for the patient with acute neurological illness. Any significant period of hypoxia may result in secondary injury to the vulnerable brain and exacerbate any ICP elevation [20, 25]. Three minutes of pre-oxygenation with noninvasive positive pressure ventilation (NIPPV) [30], or a heated high-flow nasal cannula (HHFNC) at 60–70 L/min that is continued following induction [31–33], may be more effective at preserving oxygenation during the intubation attempt than pre-oxygenation with a high-flow (non-rebreather) face mask. Pre-oxygenation should be performed with the head of bed elevated to 30°. While randomized trials have had mixed results [31, 34, 35], the preponderance of evidence suggests that apneic oxygenation, performed using either HHFNC at 60–70 L/min or a regular nasal cannula at 15 L/min during laryngoscopy, increases time to desaturation and first-pass success without hypoxia [31–33, 36]. Since apneic oxygenation is easy to perform, inexpensive, and without serious adverse effects, its use is recommended during intubation of the critically ill neurological patient.

Intubating the Patient with Intracranial Pathology

Rapid sequence intubation (RSI) consists of the simultaneous administration of a fast-active sedative to induce immediate unresponsiveness and a neuromuscular-blocking agent to achieve optimal intubating conditions, with the goal of attaining control of the airway in the critically ill patient at risk of aspiration of stomach contents. RSI limits the elevation of Intracranial Pressure (ICP) often associated with the physiologic responses to laryngoscopy and is the preferred method for intubation of the patient with elevated ICP [37–40]. The presence of coma should not justify proceeding without pharmacological agents, or administration of only a neuromuscular blocking agent without appropriate pre-treatment and induction agents. Although the patient may seem unresponsive, laryngoscopy and intubation often provoke reflexes that elevate ICP unless appropriate pre-treatment and induction agents are used [41].

Outcomes in patients with intracranial catastrophes are related to the maintenance of both brain perfusion and oxygenation. It is generally recommended that the ICP be maintained below 22 mmHg, MAP between 80 and 110 mmHg, and Cerebral Perfusion Pressure (CPP = MAP-ICP) at a minimum of 60 mmHg during intubation [42]. Because the intracranial pressure may not be known at the time of urgent intubation, clinicians should anticipate elevated ICP in patients with conditions such as mass lesions, hydrocephalus or extensive cerebral oedema, and choose an appropriate BP target accordingly. When the airway is manipulated, two responses may exacerbate intracranial hypertension. The reflex sympathetic response (RSR) results in increased heart rate, increased blood pressure, and, consequently, increased ICP. The direct laryngeal reflex stimulates an increase in ICP independent of the RSR [3]. Although the RSR may be dangerous in a hypertensive patient, pre-treatment of the RSR is not indicated in a hypotensive patient with known or suspected increased ICP [43]. Elevations in ICP should be mitigated by minimizing airway manipulation (the most experienced person should perform the intubation) and administering medications.

Common pre-medications used to prevent increased ICP during intubation include:

Lidocaine

Administered intravenously at a dose of 1.5 mg/kg 60–90 s before intubation, lidocaine attenuates the direct laryngeal reflex. There is mixed evidence that it mitigates the RSR [44, 45]. It is not associated with drop in MAP.

Fentanyl

At doses of 2–3 μg/kg, fentanyl attenuates the RSR associated with intubation, and is administered as a single pretreatment dose over 30–60 s in order to reduce chances of apnea or hypoventilation prior to induction and paralysis [46]. It is generally not used in patients with incipient or actual hypotension, or those who are dependent on sympathetic drive to maintain an adequate blood pressure for cerebral perfusion.

ICP during intubation also rises due to body positioning and hypoventilation. Hypoventilation immediately causes increased pCO_2, a potent acute cerebral vasodilator. When ICP is known or suspected to be elevated, the following approach is suggested (Fig. 3):

- Duration of time with head of bed lowered should be minimized. Reverse Trendelenberg positioning during intubation may be considered.
- MAP must be preserved throughout the procedure, with a goal of 80–100 mmHg, but not lower than the pre-intubation blood pressure. If ICP is monitored, keep CPP >60 mmHg.
- Pain, discomfort, agitation, and fear must be controlled with adequate analgesia and sedation.
- Hypoventilation must be avoided, and quantitative end-tidal capnography monitoring is recommended.

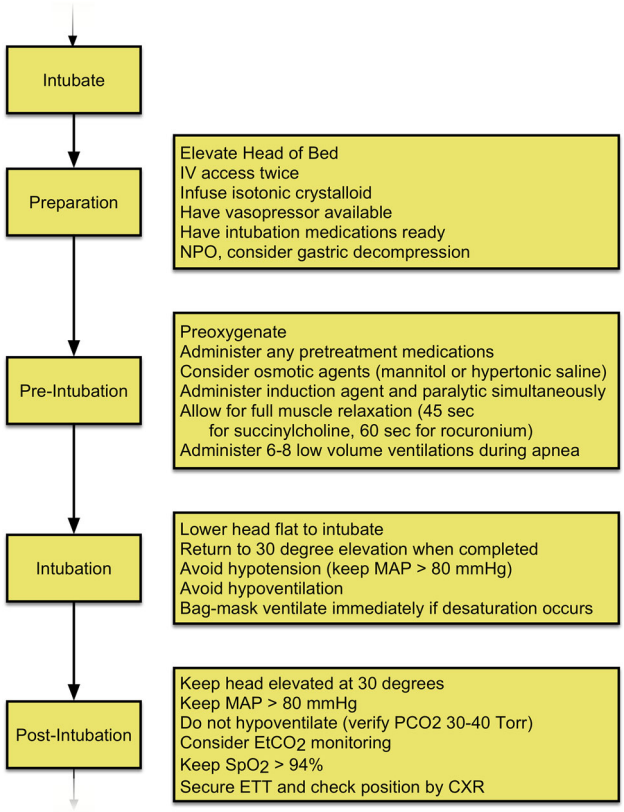
Intubate
Preparation
Elevate Head of Bed
IV access twice
Infuse isotonic crystalloid
Have vasopressor available
Have intubation medications ready
NPO, consider gastric decompression
Pre-Intubation
Preoxygenate
Administer any pretreatment medications
Consider osmotic agents (mannitol or hypertonic saline)
Administer induction agent and paralytic simultaneously
Allow for full muscle relaxation (45 sec
for succinylcholine, 60 sec for rocuronium)
Administer 6-8 low volume ventilations during apnea
Intubation
Lower head flat to intubate
Return to 30 degree elevation when completed
Avoid hypotension (keep MAP > 80 mmHg)
Avoid hypoventilation
Bag-mask ventilate immediately if desaturation occurs
Post-Intubation
Keep head elevated at 30 degrees
Keep MAP > 80 mmHg
Do not hypoventilate (verify PCO2 30-40 Torr)
Consider EtCO2 monitoring
Keep SpO2 > 94%
Secure ETT and check position by CXR

Fig. 3 Intubation with elevated ICP [212]

- Adequate oxyhemoglobin saturation should be maintained at all times during intubation. In addition to the use of effective pre-oxygenation and apneic oxygenation, bag-mask ventilation should be used between intubation attempts and at any time that the SpO2 is lower than 94%.

Intubating the Patient with Brain Ischemia

In suspected or proven ischaemic stroke, careful attention should be taken to avoid hypotension during induction and post intubation. In the healthy state, the cerebrovascular circulation is well collateralized. During ischaemic stroke, many patients possess an infarct core surrounded by a greater region of ischaemic penumbra. Under these circumstances, the ischaemic penumbra consists of a region of vasodilated vessels, receiving maximal compensatory shunting from the adjacent cerebrovascular circulation. Hypertension and tachycardia often reflect a compensatory, not pathophysiologic, response to this ischemia and may be necessary to maintain perfusion of the ischaemic territory.

Certain vasoactive agents may reverse regional vasoconstriction in normal areas of the brain that is necessary to maintain physiologic shunting of blood to the region of ischemia, even if they do not drop the systemic blood pressure or alter the global CPP. An episode of relative or actual hypotension can dramatically increase brain infarct size by "stealing" blood flow from the maximally dilated watershed territories between vascular distributions.

Brain ischemia is not limited to ischaemic stroke but is also variably present in patients with vasospasm, traumatic brain injury (TBI), intracranial and extracranial cerebrovascular stenosis, and hypoxic-ischaemic encephalopathy following resuscitation from cardiac arrest. Strong correlations between episodic hypotension and poor neurological outcome have been noted in the critical hours following resuscitation from TBI and cardiac arrest [24, 26, 47, 48]. The intubating clinician should be aware of the risks of even a transient decrease in CBF and strive to maintain CBF and systemic vascular tone during airway management. A fluid bolus should be administered prior to intubation in any patient with possible volume depletion. Ketamine or Etomidate are the preferred induction agents in patients with compromised cerebral perfusion. Vasopressors should be administered to prevent hypotension as needed during or following RSI. Brain ischemia is worsened by the effect of hyperventilation upon vascular tone. Normocapnea should be maintained during intubation, and early correlation of an arterial CO_2 sample with $ETCO_2$ is suggested to enable non-invasive tracking of ventilation [1, 49].

Conflicting evidence exists regarding the risks of routine intubation and general anesthesia for acute ischaemic stroke patients who require endovascular intervention [50–53]. Since there is some evidence to suggest harm from routine use of general anesthesia, [50, 52, 53] moderate sedation without intubation may be the technique of choice for most ischaemic stroke patients requiring endovascular therapy. Intubation should be considered, however, for patients with bulbar dysfunction, an inability to protect the airway or control secretions, hypoxia, hypercarbia, a high risk of aspiration (including patients with emesis) or significant agitation [53]. The only randomized trial of conscious sedation versus intubation in patients undergoing urgent endovascular thrombectomy for acute anterior circulation thrombosis did not show a difference in outcomes [50].

Intubating the Patient with Neuromuscular Weakness

Although some patients with neuromuscular disease require immediate intubation, those with preserved bulbar function and reasonable functional ventilatory reserves may undergo a trial of non-invasive ventilation combined

with airway clearance by the frequent use of chest physiotherapy and a cough-assist device [54–56].

Any patient with neuromuscular weakness that complains of dyspnea, should undergo an assessment of respiratory function that includes (see also the *Acute Non-Traumatic Weakness* protocol):

- Arterial blood gas measurement.
- Serial pulmonary function testing to include negative inspiratory force (NIF), vital capacity (FVC) and maximum expiratory force (MEF).
- Assessment of bulbar function, neck strength, and cough.

Candidates for intubation include patients with bulbar dysfunction and a demonstrated inability to manage airway secretions or maintain a patent airway, those who have a rapidly progressive course, and those who do not rapidly stabilize gas exchange and work of breathing with non-invasive ventilation [54].

In myasthenia gravis, succinylcholine is safe but requires approximately 2.5 times the dose to get the same effects [57]. Non-depolarizing agents such as Rocuronium are also safe but will have a prolonged duration [57]. In conditions such as Guillain–Barre, succinylcholine can precipitate life-threatening hyperkalemia, and only non-depolarizing agents should be used.

Intubating the Patient with Cervical Spine Injury

Cervical Spine injury should be suspected during direct neck trauma or blunt head trauma resulting in loss of consciousness. During care of these patients, measures must be taken to protect the spinal cord during any movements or procedures, including intubation. Airway maneuvers, including head-tilt/chin lift to achieve the sniffing position, bag-mask ventilation, cricoid pressure, and direct laryngoscopy itself, can all result in displacement of the cervical spine and injure the spinal cord when cervical instability is present [28, 58, 59]. Blade elevation results in the greatest displacement of the spine during laryngoscopy [28]. Awake fiberoptic intubation should, therefore, be considered the best option in patients with significant cervical spine injury who are awake, spontaneously breathing and have stable oxygenation on supplemental oxygen [60–63]. Patients with acute hypoxic or hypercarbic respiratory failure and rapid clinical decline may not be suitable candidates for an awake fiberoptic intubation; such patients may require RSI with manual in-line stabilization. Similarly, patients who may have raised intracranial pressure and those with impending or established cardiovascular collapse should not undergo awake fiberoptic intubation. When RSI is performed, every precaution should be taken to minimize displacement of the cervical spine, although some movement is inevitable [28, 58, 59]. Prior to intubation, the anterior part of the semi-rigid collar should be removed to permit greater mouth opening during laryngoscopy. The head should then be maintained in the neutral position using Manual In-Line Stabilization (MILS) (demonstrated in Fig. 4), in which an assistant stands by the patient with a hand on either side of the head between the mastoid process and the occiput, [58] The assistant must then hold the head steady while gently opposing the applied forces of airway manipulation.

When a basic maneuver is necessary to open the airway, a jaw-thrust, which may also cause some displacement, should be performed rather than a head-tilt/chin lift. The use of cricoid pressure is no longer recommended during intubation. It definitely should not be implemented in patients with cervical spine injury, as it may cause posterior displacement of the cervical spine [64, 65]. MILS adversely impacts visualization of the glottis, with only the epiglottis visible in about 22% of patients intubated using direct laryngoscopy (DL) [66]. The use of video laryngoscopy (VL) to improve glottic visualization has therefore become common practice when MILS is necessary [67–69]. While VL consistently results in a better view of the glottis than DL [70–75], manipulation of the ETT into the glottis can be challenging. The anterior part of the semi-rigid collar should be promptly re-applied following intubation.

Fig. 4 Manual in-line stabilization during intubation of the patient who requires immobilization of the cervical spine. Image depicts use of video laryngoscopy

Rapid Sequence Intubation

Induction Agents

Since hypotension is common following sedation [7, 17–19], and may exacerbate secondary injury in patients with acute neurological illness [20–22, 24–26], the use of a hemodynamically neutral agent such as Etomidate or a sympathetic stimulant such as Ketamine is recommended. Table 4 lists the properties of some medications commonly used for RSI in patients with acute neurological illness.

Etomidate

Etomidate is a short-acting imidazole derivative that provides sedation and muscle relaxation with minimal hemodynamic effect. Despite concerns about adrenal suppression, it is considered to be one of the most hemodynamically neutral of all commonly used induction agents and a drug of choice for patients with elevated ICP or compromised cerebral perfusion [76, 77]. While Etomidate may cause transient myoclonus and regional neuroexcitation [78, 79], the clinical relevance of these phenomena are unknown.

Ketamine

Ketamine is a dissociative agent administered at a dose of 2 mg/kg IV push. Ketamine causes sympathetic stimulation and is therefore the most favorable of all available induction agents from a hemodynamic standpoint [80–82]. It is the induction agent of choice for patients with shock or compromised cerebral perfusion. Historically, use of ketamine was avoided in patients with elevated ICP. More recent evidence suggests, however, that when concurrent sedation is provided, it is safe in patients with elevated ICP [83, 84]. In view of the significant sympathetic stimulation that accompanies its use, an alternative to Ketamine should be considered in patients with acute intracerebral hemorrhage and elevated blood pressure, unsecured vascular malformations, or significant ischaemic heart disease.

Neuromuscular Blockade

Succinylcholine

Succinylcholine is a depolarizing neuromuscular blocker with a rapid onset (30–60 s) and short duration of action (5–15 min), making it an ideal agent for RSI. The RSI dose is 1.5–2 mg/kg IV. Although it has been associated with transient increases in ICP, the effect is not considered clinically significant [85]. Immobile and chronically ill neurologic patients are at risk for succinylcholine-induced hyperkalemia, because of an upregulation in extra-junctional acetyl-choline receptors. This includes patients with chronic neurological/neuromuscular disease such as amyotrophic lateral sclerosis, multiple sclerosis and chronic myopathies, as well as those with as little as 24–72 h of immobility following acute brain or spinal cord injury [86]. It is critical, therefore, that the provider performing RSI always screen for contra-indications to succinylcholine in patients with acute neurological illness, to avoid precipitating a life-threatening bradyarrhythmia, ventricular arrhythmia or cardiac arrest. Succinylcholine should be avoided in these patients, and a non-depolarizing agent used [87].

Non-depolarizing Agents

Non-depolarizing agents have a longer duration of action than Succinylcholine. A non-depolarizing agent with rapid onset and relatively short duration of action should be used, such as Rocuronium (at 1.2–1.4 mg/kg IV push) or Vecuronium (at 0.1–0.2 mg/kg IV push). Rocuronium produces optimal intubating conditions almost as quickly (45–60 s) as Succinylcholine, but has a significantly longer duration of action (45–70 min). The novel agent Sugammedex, administered at a dose of 16 mg/kg 3 min following Rocuronium dosing, can reverse neuromuscular blockade and restore muscle function faster than with the use of Succinylcholine [88, 89]. Sugammedex should therefore be available at locations where the use of steroidal neuromuscular blocking agents such as Rocuronium is common, and can be utilized in clinical situations where a rapid return of muscle function is desirable.

Bag-Ventilation and Basic Airway Management

Following induction and paralysis, the use of proper bag-mask-ventilation (BMV) technique is critical. Two-provider BMV is preferable, with one provider entirely focused on attaining an effective mask seal while simultaneously performing a basic airway-opening maneuver, such as the head-tilt/chin-lift, or, when cervical spine immobilization is necessary, a jaw thrust (Fig. 5). A second individual performs bag-ventilation and a third provides MILS when necessary. The morbidly obese patient should be placed in the "ramped" position, with blankets stacked under the upper body and head until horizontal alignment is achieved between the external auditory meatus and the sternal notch [90]. The routine use of an adjuvant such as an oral or nasal airway may greatly facilitate effective BMV. Apneic oxygenation with a HHFNC or a regular nasal cannula at 15 L/min should be performed following induction and continued during BMV and laryngoscopy (Fig. 5).

Fig. 5 Technique of 2-provider bag mask ventilation, with a third provider performing MILS. First provider grasps the mask with the thumb and index finger in a "C" hold while the other 3 fingers grasp the mandible in an "E" hold, while performing either jaw thrust, as shown in this patient, or a head-tilt/chin-lift. A third provider provides MILS

Laryngoscopy and Intubation

When BMV is effective, up to 3 attempts at laryngoscopy and intubation are permissible, as long the SpO2 remains >94%. BMV should be performed between attempts and apneic oxygenation continued at all times. With every subsequent attempt, a change in operator (more experienced operator steps in) and/or technique (such as a change from DL to VL, or use of a bougie) should occur. When BMV using optimal technique is ineffective, an experienced operator may make a single attempt at laryngoscopy and intubation. Use of VL should be considered for this "single, best attempt" for optimal glottis visualization. The use of VL consistently results in higher rates of glottis visualization [70–75], and may be particularly valuable for less experienced operators and for difficult airways [73, 91]. Randomized trials have not, however, consistently demonstrated superiority in first-pass success rates or a reduction in episodes of hypoxia with the use of VL for intubation of the critically ill [91–95]. When intubation is performed with the Glidescope® (Verathon Medical Inc, Bothell, WA, USA) VL, use of the highly curved rigid Glidescope® stylet is recommended, to facilitate navigation of the ETT past the sharp curve of the VL blade to the glottis [96].

The Cormack-Lehane system is used to grade the direct laryngoscopic view of the glottis [97, 98].

Grade 1—Entire glottis visible.
Grade 2a—Partial view of the glottis.
Grade 2b—Only the posterior extremity of the glottis (or only arytenoids) visible.
Grade 3—Only epiglottis visible, no view of glottis inlet.
Grade 4—Neither epiglottis nor glottis visible.

Documentation of the direct laryngoscopic grade in the medical record is critical, to inform future airway management decisions.

The Failed Airway

A failed airway is considered to exist in one of two situations—(1) the "cannot intubate, cannot ventilate" scenario, when BMV is ineffective at achieving gas exchange and a "single, best attempt" at intubation by an experienced operator is unsuccessful, and (2) the "cannot intubate, CAN ventilate" scenario, when 3 attempts at intubation (at least one by an experienced operator) using best equipment (including VL) and technique have been unsuccessful, but BMV remains effective. Since both these scenarios may result in death or devastating anoxic injury [6, 7], every provider who participates in airway management of the critically ill neurological patient must have a basic knowledge of the approach to a failed airway. In order to provide the most direct and dependable path to a definitive airway, the ENLS intubation algorithm recommends an attempt at placement of a supraglottic airway (SGA), such as a Laryngeal Mask Airway, in the event of a failed airway. SGAs have a high success rate with inexperienced providers and typically require limited training to use [99, 100]. Second generation SGAs, that include features such as a bite-block and an esophageal/gastric channel, or SGAs that can serve as conduits for subsequent blind or fiberoptic-guided passage of an ETT, are preferable [101]. Up to 2 attempts, with different operators and/or techniques, are permissible as long as the SpO2 remains >94%. Apneic oxygenation should be continued and BMV performed between attempts. If SGA placement is successful and gas-exchange established, insertion of an ETT through the SGA may be attempted. Alternatively, an urgent tracheostomy should be performed. When SGA insertion is unsuccessful, or oxygen desaturation occurs at any time, immediate cricothyroidotomy should be performed, using a surgical or percutaneous technique. Delays in performing a cricothyroidotomy in patients with a failed airway are an important cause of death and severe morbidity [6, 7].

Post-intubation Management

Figure 1 lists tasks to be performed following intubation [102].

Basic Ventilator Settings

Immediately following intubation, respiratory and hemodynamic homeostasis should be restored. Except in situations of acute brain herniation, the goals of mechanical ventilation are:

- Normalization of oxygenation utilizing the lowest FiO_2 that will maintain hemoglobin saturation $>94\%$.
- Normalization of ventilation to achieve a systemic pH of 7.3–7.4, and pCO_2 or $ETCO_2$ to 30–40 mmHg.
- Normalization of the work of breathing.
- Prevention of ventilator induced lung injury.

In most circumstances, clinicians should default to volume-cycled ventilation at 6–8 cc/kg of ideal body weight and a respiratory rate of 12–14 per minute. However, these settings must take into account the patient's minute ventilation prior to intubation. Normal pCO_2 is an appropriate target unless there is chronic hypercarbia (i.e., severe COPD or sleep-disordered breathing). In situations of chronic hypercarbia, the admission bicarbonate level should be used to estimate the "baseline" pCO_2, and that level should subsequently be used as the target. When metabolic acidosis is present, ventilation should target normal pH.

Titrate Ventilation

Induced Hyperventilation: Ventilation, Carbon Dioxide Tension, and Clinical Outcome

Hyperventilation causes cerebral vasoconstriction and decreased CBF, while hypoventilation causes cerebral vasodilation and increased ICP [103]. Dysventilation (and especially hyperventilation) is associated with poor outcomes in traumatic brain injury (TBI) [104–106]. The Brain Trauma Foundation recommends targeting eucapnea in patients with brain trauma [42].

However, the relationship between arterial and central pH and pCO_2 is complex and incompletely understood. During concomitant metabolic acidosis and TBI, CNS pH and CBF are often preserved despite severe systemic acidosis due to the blood brain barrier and the central nervous system (CNS) buffering capacity [107]. Alternatively, in patients with chronic respiratory acidosis, the set-point of cerebral CO_2 reactivity changes. It is therefore recommended that mechanical ventilation be adjusted to correct the pH and not the pCO_2, or that the estimated "pre-morbid" pCO_2 target be used (see Table 2 below). This is a practical goal since ventilating these patients to "normal" pCO_2 targets may be extremely difficult or impossible when obstructive lung disease is present.

Herniation: Intentional Hyperventilation to Treat Brain Herniation and Increased ICP

When a patient develops brain herniation with elevated intracranial pressure, hyperventilation is an appropriate temporizing intervention designed to acutely decrease ICP and prevent subsequent neuronal injury and death [108, 109]. Maximal cerebral vasoconstriction is achieved at a pCO_2 near 20 mmHg. Therefore, hyperventilation below this level results in no further therapeutic advantage and even less profound pCO_2 reductions may impede venous return to the heart, decrease blood pressure, and exacerbate cerebral hypoperfusion.

During hyperventilation, end tidal CO_2 monitoring (quantitative capnography) is suggested. As soon as other treatments to control ICP are in place (e.g., blood pressure support, osmotherapy, surgical decompression, hypothermia, metabolic therapy), hyperventilation should be weaned to restore brain perfusion [110].

Hyperventilation for increased ICP is not safe or effective when employed for a prolonged period [42, 111, 112]. Hyperventilation severely reduces CBF, increases the volume of ischaemic tissue, and, may result in rebound elevation of ICP during weaning [113–115]. When prolonged (mild) hyperventilation is employed, it is strongly recommended that end-tidal CO_2 and cerebral metabolic monitoring (jugular oximetry, CBF, brain tissue oxygen, or cerebral microdialysis) be used to verify the adequacy of tissue perfusion.

Acidemic and Alkalemic Hypocarbia: Potential for Suppression of Spontaneous Hyperventilation

There are two circumstances that should be considered in patients with spontaneous hypocarbia: those whose response to systemic metabolic acidosis accounts for their high ventilatory demand, and those (alkalotic) patients in whom ventilation exceeds systemic metabolic needs.

In patients whose ventilation is driven by metabolic acidosis, suppression of the respiratory drive with sedation

Table 2 Chronic respiratory acidosis: estimated pre-morbid pCO_2 based on admission HCO_3 level

Chronic respiratory acidosis: estimated pre-morbid pCO_2 based on admission HCO_3 level								
Admission bicarbonate	45	42	39	36	33	30	27	24
Predicted "usual" pCO_2	92.5	85	77.5	70	62.5	55	47.5	40

or neuromuscular blockade is not recommended, unless direct measurement of brain chemistry suggests that hyperventilation is driving cerebral metabolic crisis. Under these circumstances, clinicians must find another means to buffer pH.

Mechanically ventilated TBI patients presenting with hypocarbia have worse outcomes than their normocarbic peers. However, non-intubated patients presenting with hypocarbia do not exhibit similar findings, suggesting that hypocarbia, in this setting, may be a physiologic response and should not be suppressed [105].

Despite decades of observation and consideration, little is known about alkalemic hypocarbia in patients with an acute brain injury. Alkalemic hypocarbia following brain injury may be theoretically explained by a variety of physiologic and pathophysiologic mechanisms, more than one of which may be present in an individual patient:

- Brain tissue acidosis requiring acute hyperventilation as a buffer until CNS bicarbonate-generating compensatory mechanisms can catch up.
- Inadequately treated pain, anxiety, fear, or agitation.
- Fever.
- Auto-regulation of elevated ICP.
- Heme breakdown products or a lactic acid load in the ventricular system.
- Direct pressure on chemoreceptors present in the floor of the 4th ventricle.
- Physiologic dysregulation of the medullary respiratory rhythm generator, which has afferent inputs from the pons, mesencephalon, and higher cortical centers.

A recent trial of patients with severe brain injury monitored for brain tissue oxygen showed brain tissue hypoxia worsened when $EtCO_2$ values were reduced by spontaneous alkalemic hyperventilation, suggesting possible harm [116]. It is rarely known whether alkalemic hypocapnia is a physiologic or pathophysiologic process, suppression of this respiratory activity is recommended only in response to evidence that hyperventilation is causing direct harm, either by inducing cerebral ischemia or indirectly by increased systemic metabolic demands and work of breathing.

Oxygenation and Outcomes

Hypoxia is a major source of secondary brain injury [117], and the injured and ischaemic brain is particularly vulnerable to low oxygen levels. Similarly, supra-physiologic levels of oxygen provided to acutely ill patients have the potential to worsen reperfusion injury and outcomes [118, 119]. Hyperoxia drives the formation of reactive oxygen species, overwhelming antioxidants at sites of tissue injury; directly injures respiratory epithelium and alveoli inducing inflammation; drives hypercarbia; and leads to absorption atelectasis in the lung. Hyperoxia ($PaO_2 > 300$ mmHg) immediately following resuscitation is independently associated with poor outcomes in traumatic brain injury (TBI) and cardiac arrest [119, 120], though not all published data are in accordance [121–123].

It is recommended that 100% oxygen be provided for pre-oxygenation immediately prior to intubation, but that oxygen be immediately weaned following intubation to 50%, or the lowest FiO_2 that will support an oxyhemoglobin saturation of 95–100%. This normoxic resuscitation strategy is recommended in the 2010 American Heart Association Guidelines for post-resuscitation care after cardiac arrest [121].

Oxygenation and Ventilation Monitoring

Oxygenation should be monitored by pulse oximetry or by arterial blood gas analysis when oximetry is suspected to be inaccurate. Conditions of poor perfusion to the extremities, acidosis, vasopressor use, anemia, carboxyhemoglobinemia and methemoglobinemia, and hypoxia all have the potential to compromise the accuracy of pulse oximetry measurements [124].

Ventilation is traditionally monitored by serial arterial blood gas analysis, though venous blood gas analysis may provide an adequate surrogate when arterial samples cannot be obtained. End tidal quantitative capnography of exhaled gases provides an appealing continuous measurement and is extremely useful to monitor trends in ventilation. One study showed that severely hyperventilated head trauma patients ($pCO_2 < 25$ mmHg) in the prehospital environment had higher mortality, and that use of quantitative capnography by paramedics significantly decreased the incidence of hyperventilation [125]. A similar study in patients with major trauma showed a much higher incidence of "normocapnea" on hospital arrival when $ETCO_2$ was monitored by medics.

Because $ETCO_2$ measurements reflect not only ventilation but also systemic perfusion, the correlation between $ETCO_2$ and pCO_2 in the blood is variable, especially when severe physiologic derangements are present [126]. In an inpatient environment, $ETCO_2$ measurements should always be correlated with an arterial pCO_2 sample. ETCO2 and pCO_2 may also vary significantly when lung disease and ventilation-perfusion mismatch are present [127].

Lung Injury

Patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) are vulnerable to lung injury known variably as ventilator induced lung injury (VILI) or ventilator associated lung injury (VALI). ALI and ARDS represent a spectrum of disease characterized by bilateral parenchymal pulmonary infiltrates, significant hypoxia, absence of left ventricular dysfunction, and hyperacuity of onset [128]. These patients often require high levels of oxygen and elevated mean airway pressures to achieve adequate gas exchange.

Patients with ALI and ARDS often have high circulating levels of inflammatory mediators, which are associated with injury to other vital organs, and are exacerbated by injurious techniques of ventilation. VALI is thought to be caused by:

- Barotrauma: induced by high ventilator pressures, particularly a high plateau pressure.
- Volutrauma: induced by higher tidal volumes, often despite low ventilator pressures.
- Atelectrauma: shearing injury due to recurrent opening and closing of alveolar sacs that may lack adequate surfactant.
- High inspired fraction of oxygen.
- High levels of circulating inflammatory cytokines.

Many modes and techniques of ventilation have been proposed to manage the severe gas exchange abnormalities associated with ARDS, though only a few important issues are covered here.

Patients with ALI or ARDS should be ventilated using a strategy of low tidal volumes (6 cc/kg), low plateau pressures (<30 mmHg), adequate positive end expiratory pressure (PEEP) to prevent cyclic collapse of alveolar units, and inhaled oxygen fraction rapidly weaned to 0.6 or less.

Although the landmark study of low tidal volume mechanical ventilation emphasizes permissive hypercarbia, [128] elevation in carbon dioxide is a potent modulator of CBF and this strategy must be balanced with concerns for intracranial hypertension [129]. Several small studies suggest that lung protective ventilation strategies causing mild hypercarbia in patients with elevated ICP may be tolerated [129, 130], but more data are needed before this may be considered safe in routine practice. Prone positioning may increase ICP [131], although several studies show that a small increase in ICP may be more than offset by dramatic improvements in oxygenation [132].

When lung compliance is low, airway pressure has the potential to be transmitted to the intrathoracic vessels and indirectly increase ICP. Although this physiology was once used to justify low-PEEP ventilation in patients with head injury, subsequent research has shown PEEP in brain injured patients to be well tolerated, especially when lung compliance is poor and adequate blood pressure is maintained [133, 134]. Ventilation without PEEP is discouraged, due to the likelihood of atelectrauma. However, the relationship of airway pressure to ICP, CPP, and cerebral perfusion is of concern, and should be individually reviewed based on each patient's physiology [135–138].

Sedation

Recent guidelines have reviewed the management pain, agitation and delirium in the critically ill [139].

Necessity of Sedation

Sedation use in the critically ill neurological patient has both benefits and drawbacks. Sedation may be needed to alleviate fear and anxiety, reduce ICP and cerebral oxygen consumption, facilitate tolerance of the endotracheal tube and mechanical ventilation, or to reduce sympathetic nervous activity. Complications associated with undersedation include ventilator dysynchrony, patient injury, agitation, anxiety, device removal, and elevated ICP [140–153]. Adequate sedation is paramount in all therapeutic algorithms for the treatment of increased ICP [144, 145], since psychomotor restlessness, pain, and autonomic stress all adversely affect ICP, CBF, CPP, and the cerebral metabolic rate for oxygen metabolism ($CMRO_2$). Conversely, sedation makes accurate neurological examination, the cornerstone of clinical assessment, difficult or impossible. Therapeutic and procedural decision making are often contingent upon an accurate neurological assessment. Acute changes in brain physiology become difficult to detect, and the accuracy of neuroprognostication is decreased [138, 154]. Sedation may cause vasodilation, reducing cerebral perfusion due to hypotension and also reversing physiologically advantageous shunting of blood into areas of ischemia. Even short-acting sedatives are known to accumulate in fatty tissues, causing effects beyond their intended duration. Despite each of the competing interests, adequate consideration must be made for patient comfort (Tables 3, 4).

Depth of Sedation and Sedation Interruption

In a general intensive care unit (ICU) population, the use of excessive sedation and analgesia contributes to increased duration of mechanical ventilation, longer length of stay in the ICU and hospital [146–149], increased rates of depression, post-traumatic stress disorder, infections, and long-term neurocognitive impairments [149–151].

Table 3 Airway, ventilation, and sedation communication regarding assessment and referral

Communication
☐ Mental status and neurological examination immediately pre-intubation
☐ Vitals, hemodynamics, and gas exchange pre- and post-intubation
☐ Ease of intubation and ETT position confirmation
☐ Ventilation targets and $ETCO_2$ when appropriate
☐ Analgesia and sedation strategy

Table 4 Medications commonly used in rapid sequence intubation

Drug	Dose	Onset of action	Duration of effect (min)	Indications	Precautions
Fentanyl	2–3 μ/kg IV push over 1–2 min	Within 2–3 min	30–60	Pre-induction, blunts ICP rise	Respiratory depression, hypotension, rare muscle wall rigidity
Lidocaine	1.5 mg/kg IV 2–3 min before intubation	45–90 s	10–20	Pre-induction, blunts ICP rise	Avoid if allergic or high grade heart block if no pacemaker
Esmolol	1–2 mg/kg IV	2–10 min	10–30	Pre-induction, blunts ICP rise	Bradycardia, hypotension, increased airway reactivity
Etomidate	0.3 mg/kg IV push	30–60 s	3–5	Induction, sedation; good in hypotension. Decreases CBF, ICP, preserves CPP	Decreases seizure threshold, decreases cortisol synthesis; avoid in sepsis
Propofol	2 mg/kg IV push	9–50 s	3–10	Induction, sedation, reduces ICP and airway resistance, anticonvulsive effects	Hypotension, myocardial depression
Ketamine	1.5–2 mg/kg IV push	1–2 min	5–15	Induction, analgesia, sedation, amnesia, bronchodilatory effects; good in hypotension	Catecholamine surge, possible increase in ICP, "re-emergence" phenomenon if not pretreated with benzos
Thiopental	3 mg/kg IV push	30–60 s	5–30	Normotensive, normovolemic status epilepticus or increased ICP pts	Hypotension, bronchospasm
Succinylcholine	1.5–2 mg/kg IV	30–60 s	5–15	Preferred paralytic unless contraindicated	Avoid in hyperkalemia, myopathy, neuropathy/denervation, history of malignant hyperthermia
Rocuronium	1.2 mg/kg	45–60 s	45–70	Paralysis when succinylcholine contraindicated	Caution in DMV and DI
Vecuronium	0.2 mg/kg	Within 3 min	35	Least preferred paralytic for RSI	This dose speeds onset during RSI Caution in DMV and DI

Therefore, while some patients with acute neurological illness will require deep sedation for the control of ICP or the management of status epilepticus, most patients should be lightly sedated, so they are easily arousable and attend to voice, to the extent their neurological injury permits. Sedation should be titrated to a validated sedation score, such as the Richmond Agitation Sedation Scale (RASS, Table 5) [155, 156], or the Riker Sedation Agitation Scale (SAS) [157]. A recent review of sedation assessment tools in the neurocritical care setting concluded that the SAS and Richmond Agitation Sedation Scale (RASS) are valid and useful for patients in the neurointensive care unit [158]. A goal RASS of 0 to −2 (light sedation) is recommended for most patients without a specific indication for deep sedation [139]. Sedation should be titrated to an electrophysiological endpoint when neuromuscular blockade is employed or burst-suppression is desired.

Randomized controlled trials demonstrate that protocols requiring decreases in sedative doses or daily interruption of sedative and analgesic drugs can reduce lengths of mechanical ventilation and ICU stay and reduce drug doses administered [146–148]. It is important to recognize that

Table 5 The Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 s) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

these trials did not include patients who required uninterrupted sedation, such as those with status epilepticus and refractory intracranial hypertension. Patients withdrawing from alcohol, benzodiazepines or other substances may also not tolerate abrupt interruption of sedation. While daily sedation lowering in these patient populations is not therapeutically prudent, patients without these conditions should undergo daily sedation interruption, along with a spontaneous breathing trial when appropriate.

Role of Analgesics

Unless deep sedation or general anesthesia is desired, analgesia should precede sedation. Many patients with adequate pain control do not require sedation, and, conversely, most sedative medications provide no analgesia. Sedation without pain control may be an important cause of delirium. Infusion of short acting analgesics allows for interruption and neurological assessment at intervals. Recent studies have demonstrated that analgosedation, a strategy that focuses on using a short-acting opioid infusion (Remifentanil or Fentanyl) alone to manage pain and discomfort, without a sedative, may result in a reduction in duration of mechanical ventilation and ICU length of stay [152, 159–161]. The use of analgosedation should therefore be considered first in all mechanically ventilated patients who do not have a specific indication for a sedative infusion, such as raised ICP, seizures or ongoing use of neuromuscular blockade.

Choice of Sedative

Many patients are likely to require ongoing sedation despite the effective use of analgesia. Several randomized trials have compared the use of benzodiazepine infusions, mostly Midazolam, to Propofol and Dexmedetomidine. A meta-analysis of these studies suggests that both Propofol and Dexmedetomidine are associated with shorter ICU length of stay and duration of mechanical ventilation compared to benzodiazepine infusions [139]. Either Dexmedetomidine or Propofol should therefore be utilized as a first-line agent for continuous sedation, rather than a benzodiazepine.

Non-pharmacological Strategies

Environmental stimuli are important triggers of anxiety and agitation. Providing a calm and reassuring environment, with attention to day-night cycles, restriction of noise, use of appropriate music, and/or the reassuring presence of friends and family may decrease agitation and anxiety [162]. These environmental measures are especially important when a dominant-hemisphere lesion causes aphasia and attempts at verbal communication generate agitated behaviors. The use of "sitters" to re-direct and re-orient confused or agitated patients is preferred to the use of sedating medications. Patients with acute brain injury often have deficits in short term memory, concentration, and emotional control, and their confusion may cause agitation. Confused patients require gentle and repeated re-orientation to situation and circumstances, which may obviate the need for sedation [162].

Common Sedatives in Neurological Intensive Care

Propofol

Propofol is among the best studied sedative agents used in neurological critical care. Pharmacologically, its lipid formulation allows for rapid penetration of the blood brain barrier, resulting in rapid onset and cessation of action. It has potent and immediate depressant effects on cerebral electrical and metabolic activity, and it does not require renal or hepatic metabolism for elimination. Disadvantages include robust vasodilating and hypotensive effects, considerable intravenous lipid load, and the potential for the

rare, but frequently fatal, propofol infusion syndrome. This syndrome is characterized by acidosis, hepatic failure, hypertriglyceridemia, and elevated creating kinase level. Propofol infusion syndrome may be fatal and is more common in children and adults when used at higher doses [163]. A recent study, comparing propofol to dexmedetomidine sedation in the neurocritically ill, found high (30%) incidences of hypotension in both groups [164]. Caution must be utilized with these medications when concerns for brain ischemia are present.

Remifentanil

Remifentanil hydrochloride is a mu-opioid agonist exhibiting analgesic effects with a rapid onset and a short duration of action. It is an agent which can be used as part of a combined sedative analgesic approach. A recent mechanistic review suggests that remifentanil may be a cost effective sedative alternative when ICU length of stay is considered [152]. Superiority over fentanyl has not been demonstrated [159].

Benzodiazepines

Midazolam is an appealing sedative option given the rapid onset of action and short duration of effect with bolus administration—making it an ideal agent for procedural sedation. Additionally, due to its potent gamma-aminobutyric acid (GABA) activity and relatively benign hemodynamic profile, midazolam is an important drug in treatment of refractory status epilepticus. As a long-term sedative for general ICU use, midazolam accumulates in adipose tissues, significantly prolonging duration of action unless interruptions or down-titration of dose are routinely utilized.

Bolus-dose midazolam is a good choice for intermittent agitation in a NICU population. Conversely, midazolam infusion has been associated with prolonged mechanical ventilation [139, 164]. Though most studies suggest the impact of midazolam on hemodynamics is similar compared to dexmedetomidine or propofol, a recent report suggests less instability compared to dexmedetomidine [164].

Lorazepam is a longer acting benzodiazepine. The strong GABA activity of lorazepam suppresses electrical and metabolic brain activity. Unlike midazolam, lorazepam is formulated in propylene glycol, which can accumulate to toxic levels causing metabolic acidosis and kidney injury. At lorazepam infusion rates above 3 mg/h or daily doses approaching 1 mg/kg, the osmolar gap should be followed, and alternative agents should be used if the osmolar gap rises above 10–12 mOsm/L [165, 166].

Dexmedetomidine

Dexmedetomidine is a centrally acting alpha agonist similar to clonidine, but more specific for the alpha-2 receptor. It is increasingly utilized for ICU sedation. Desirable properties include rapid onset and termination of activity, mild to moderate sedation without significant respiratory depressant action, analgesic effects, and less delirium than the benzodiazepines [164, 167]. Undesirable properties include a high incidence of bradycardia and hypotension [164, 167].

Barbiturates

Use of barbiturates as a sedative in the neurocritical care unit is limited due to its undesirable side effect profile. Immunosuppressant properties and negative inotropic effects are amongst the more concerning limitations. Barbiturates remain second-line therapy for the control of ICP after propofol. They remain in widespread use to control refractory status epilepticus, and their potent effects on cerebral metabolic and electrical activity make them an appealing class of agents for sedation in the NICU. Pentobarbital serves as a potent agent for deep sedation in patients with refractory *status epilepticus* or elevated ICP [168–170].

No tools for the assessment of delirium have been validated in neurocritical care patients, though several studies that used the Intensive Care Delirium Screening Checklist enrolled NICU patients [171, 172].

Many studies have addressed the sedation monitoring approaches and medication choices for NICU patients. One prospective, randomized trial of 67 mechanically ventilated adult patients sedated with propofol showed that the bispectral index (BIS) monitor added to routine sedation scale monitoring significantly reduced the propofol dose and the time to awakening when compared to subjective scale monitoring alone [173].

Pediatric Considerations

Anatomical and physiological differences alter the approach to intubation and mechanical ventilation of children suffering from neurologic injury. While cervical spinal injury is uncommon in children, approximately half of all cervical spinal injuries are associated with simultaneous traumatic brain injury (TBI) [174]. Therefore, cervical spine precautions should be taken when intubating a child with suspected TBI. Criteria for tracheal intubation of children with TBI and other forms of acute brain injury include hypoxemia unresponsive to supplemental oxygen, apnea, hypercarbia ($PaCO2 > 45$ mmHg), Glasgow Coma

Scale Sore (GCS) ≤8, rapid decrease in GCS, anisocoria >1 mm in the context of altered mental status, spinal injury compromising ventilation, abnormal airway reflexes, and any clinical signs of herniation syndrome [175]. A pediatric version of the GCS is recommended when evaluating children infants with acute brain injury.

Several anatomical differences between the pediatric and adult airway should be considered prior to intubating. Children have a proportionally larger tongue, more compliant epiglottis and upper airway tissues, and a prominent occiput. Positioning can be optimized by placing a small shoulder roll prior to intubation. The infant larynx is more anterior and cephalad (C3–4 vs. C4–5 in adults). The narrowest part occurs at the cricoid ring gives a cone shaped appearance that does not become cylindrical until approximately 8 years of age [176]. Pediatric Advanced Life Support Guidelines advise that oral intubation should be performed while maintaining spine immobilization using a cuffed ET tube in children with TBI [177]. Cuff pressures should not be greater than 20 cm H2O due to the risk of mucosal ischemia [178]. A multi-center, randomized control trial demonstrated no increase in post-extubation stridor or long-term complications when using cuffed tubes [179]. For un-cuffed ET tube sizing in children (if cuffed is not available) use the age-based formula: 4+ (age in years/4) [180–182]. If inserting a regular cuffed ET tube, select one full size smaller than determined by the age-based formula [116]. If placing a micro-cuffed ET tube, select a tube one half size smaller than the age-based calculation [180–182]. A stylet bent in a hockey stick configuration can help reinforce the rigidity of small ET tubes and help direct them anteriorly through the glottis [183].

When intubating a child less than 2 years old, a straight laryngoscope blade directly lifting the epiglottis may be preferred because of the infant's large and acutely angled epiglottis. Generally, a straight size 00 laryngoscope blade is appropriate for extremely premature infants, a size 0 for average-sized newborns, a size 1 for most infants beyond the immediate newborn period, and a size 2 blade for children over the age of two. If an appropriately sized ET tube is placed, the ideal depth can be achieved by inserting the tube until the centimeter marking at the lip is three times the internal diameter of the ET tube [184].

It is prudent to assume a full stomach and a cervical spinal injury when intubating a child with TBI. Endotracheal intubation should utilize a cerebral-protective rapid sequence induction with cricoid pressure and pre-oxygenation. Bag-valve-mask ventilation should not be attempted unless the child has apnea, hypoxemia, or signs of impending herniation. However, the time to desaturation following pre-oxygenation is shorter in apneic infants compared to older children (less than 100 s), and a modified RSI technique with gentle pressure-limited mask ventilation (10–12 cm H2O) and 100% oxygen may be used to avoid hypoxemia [185, 186]. This technique may also limit hypercarbia and keeps small airways open without the risk of gastric inflation and related morbidity [187–189]. Cricoid pressure is routinely applied despite questionable evidence that it improves clinical outcomes [188, 190, 191].

Pretreatment with lidocaine (1.5 mg/kg IV with max dose 100 mg) may be used but its administration should not delay emergent intubation [192]. Atropine (0.02 mg/kg IV with minimum dose 0.1 mg and max single dose 0.5 mg) is recommended in children ≤1 year old or children <5 years old receiving succinylcholine [193]. For hemodynamically unstable children, the combination of etomidate (0.2–0.6 mg/kg) and neuromuscular blockade with rocuronium (1 mg/kg) or vecuronium (0.3 mg/kg) IV is often used. The association between etomidate administration and clinically significant adrenal insufficiency is not well established in children but can be considered when selecting optimal medications for intubation. Succinylcholine is sometimes avoided because of the risk of malignant hyperthermia possible ICP elevation hyperkalemia, and life threatening complications associated with unknown occult metabolic or neuromuscular disease [194–196]. Fentanyl (2–4 mg/kg) or ketamine (1–2 mg/kg) IV are alternative sedatives, and recent pediatric studies show that ketamine does not increase ICP and may be neuroprotective [82, 197, 198]. If hemodynamically stable, midazolam (0.1–0.2 mg/kg) can be added to any of the above combinations.

Children less than 6 months old have immature liver metabolism, which places them at high risk for respiratory depression secondary to narcotic administration [199]. Continuous infusions of propofol, especially over a 24 h period, have been associated with lethal cases of propofol infusion syndrome (metabolic acidosis and death). Therefore, continuous infusion of propofol is not recommended for pediatric patients with acute brain injury [200, 201]. Finally, while information is currently limited, concern exists regarding the potential neurotoxicity of sedatives on the developing brain [202]. The strongest evidence for this comes from animal models, with limited evidence in clinical studies [203–207].

After successful intubation, oxygen saturation of 100% and normocarbia (35–39 mmHg) should be confirmed by arterial blood gas. Unless the child has signs of herniation, prophylactic hyperventilation (PaCO2 <35 mmHg) should be avoided [208]. Adequate blood pressure must always be maintained when administering sedatives to assure adequate cerebral perfusion pressure (CPP). A CPP between 40 and 50 mmHg is recommended for children with severe TBI, with infants at the lower end of this range

and adolescents at the upper end [175]. Many studies have demonstrated that a CPP $\leq$ 40 mmHg is associated with higher mortality and morbidity [209, 210]. However, optimal age appropriate CPP thresholds have not been established for TBI and other acute neurological diagnoses. Furthermore, abnormal cerebrovascular autoregulation, which is more common in children less than 4 years old [211], makes establishing such thresholds difficult in the absence of advanced neuromonitoring.

Prophylactic interventions such as hyperosmolar therapy and hyperventilation are not recommended in the absence of signs or symptoms of herniation or neurological deterioration. In children with refractory intracranial hypertension, transient aggressive hyperventilation or barbiturate administration may be useful. Additional sedation and analgesia, together with prophylactic administration of lidocaine (1 mg/kg IV), may prevent blunt rises in ICP during ET tube suctioning.

Communication

When communicating patient information to an accepting or referring physician, consider including the key elements listed in Table 3.

Appendix 1: The 3-min Pre-intubation Neurological Assessment Checklist

Level of arousal and interaction
Basic Cortical functions
Visual field deficits
Gaze
Language
Neglect/inattention
Cranial nerves
Pupils
Corneal reflex
Eye movements
Facial symmetry
Gag
Cough
Motor function
Face and each extremity
Sensation
For symmetry
Tone
Neck and each extremity
Reflexes
Evidence of subtle or gross seizure activity
Cervical spine tenderness

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